



PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

GRASS et al.

Art Unit: 1631

Serial No.: 09/786,361

Filed: March 14, 2001

Attorney Docket No. 109904-00015

For: PHARMACOKINETIC-BASED DRUG DESIGN TOOL AND METHOD

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
Washington, D.C. 20231
Sir:

July 17, 2001

Pursuant to 37 CFR §1.56, the attention of the Patent and Trademark Office is hereby directed to the information item(s) listed on the attached PTO-1449. Unless otherwise indicated herein, one copy of each item(s) is attached. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the item(s) be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

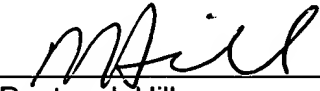
1. This Information Disclosure Statement is being filed (a) within three months of the U.S. filing date, OR (b) before the mailing date of a first Office Action on the merits in the present application, OR (c) accompanies a Request for Continued Examination. No certification or fee is required.
2. The Examiner's attention is directed to co-pending U.S. Patent Application Nos. 09/786,362 filed March 14, 2001; 09/320,544 filed May 26, 1999, 09/320,545, filed May 26, 1999; 09/320,371, filed May 26, 1999; 09/320,069, filed May 26, 1999; 09/320,270 filed May 26, 1999; and 09/320,372 filed May 26, 1999, which are directed to related technical subject matter. The identification of these U.S. Patent Applications are not to be construed as a waiver of secrecy as to those applications now or upon issuance of the present application as a patent. The Examiner is respectfully requested to consider the cited applications and the art cited therein during examination of the present application.

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3. In addition to the references already cited in this application, those cited in the applications identified above, and those cited in the associated PCT applications (international search reports, written opinions, and preliminary examination reports are included in this IDS), Applicants, due to the number of references cited, would like to point out that an article by one of the inventors, Grass, George, "Simulation models to predict oral drug absorption from in vitro data", Advanced Drug Delivery Reviews, (1997) Vol. 23, pp. 199-219, appears to be one of the more relevant references.

Respectfully submitted,



Rustan J. Hill
Registration No. 37,351

Customer No. 004372
ARENT FOX KINTNER PLOTKIN & KAHN, PLLC
1050 Connecticut Avenue, N.W.
Suite 600
Washington, D.C. 20036-5339
Tel: (202) 857-6000
Fax: (202) 638-4810
RJH/tmc

Section A

<u>NUMBER</u>	<u>FILING DATE</u>
60/100,224	14 September 1998
60/100,290	14 September 1998
60/109,232	18 November 1998
60/109,234	18 November 1998

Section B

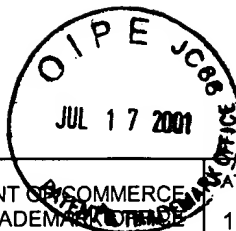
<u>APPLICATION SERIAL NUMBER</u>	<u>FILING DATE</u>	<u>STATUS</u>
09/320,069	26 May 1999	Pending
09/320,270	26 May 1999	Pending
09/320,371	26 May 1999	Pending
09/320,372	26 May 1999	Pending
09/320,544	26 May 1999	Pending
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Sheet 1 of 16



FORM PTO-1449

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ATTY. DOCKET NO.

SERIAL NO.

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LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

APPLICANT

GRASS, et al.

FILING DATE

Mach 14, 2001

GROUP

1627

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

AA	Artursson et al., "Caco-2 Monolayers in Experimental and Theoretical Predictions of Drug Transport", <u>Advanced drug Delivery Reviews</u> (1996) Vol. 22, pp 67-84
AB	Audus et al., "The Use of Cultured Epithelial and Endothelial Cells for Drug Transport and Metabolism Studies", <u>Pharmaceutical Research</u> (1990) Vol. 7, No. 5, pp 435-451
AC	Bailey et al., "The Use of the Intestinal Epithelial Cell Culture Model, Caco-2 in Pharmaceutical Development", <u>Advanced Drug Delivery Reviews</u> (1996) Vol. 22 pp. 85-103
AD	de Boer et al., "Reconstitution of the Blood-Brain Barrier in Cell Culture for Studies of Drug Transport and Metabolism", <u>Advanced Drug Deliver Reviews</u> (1996) Vol. 22, pp. 251-264
AE	Friedberg et al., "Recombinant DNA Technology as an Investigative Tool in Drug Metabolism Research", <u>Advanced Drug Delivery Reviews</u> (1996) Vol. 22, pp. 187-213
AF	Grass et al., "Mechanisms of Corneal Drug Penetration III: Modeling of Molecular Transport", <u>Journal of Pharmaceutical Sciences</u> , (1988) Vol. 77, No. 1, pp. 24-26
AG	Grass et al., "In Vitro Measurement of Gastrointestinal Tissue Permeability Using a New Diffusion Cell", <u>Pharmaceutical Research</u> (1988) Vol. 5, No. 6, pp. 372-376
AH	Hidalgo et al., "Characterization of the Unstirred Water Layer in Caco-2 Cell Monolayers Using a Novel Diffusion Apparatus", <u>Pharmaceutical Research</u> (1991) Vol. 8, No. 2, pp. 222-227
AI	Hidalgo et al., "Letter to the Editor: A New Side-by-Side Diffusion Cell for Studying Transport Across Epithelial Cell Monolayers", <u>In Vivo Cell. Dev. Biol.</u> (1992) Vol. 28A, pp. 578-580
AJ	Hidalgo et al., "Carrier-Mediated Transport and Efflux Mechanisms in Caco-2 Cells", <u>Advanced Drug Delivery Reviews</u> (1996) Vol. 22, pp. 53-66

EXAMINER

DATE CONSIDERED

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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PATENT AND TRADEMARK OFFICE

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109904-00015

09/786.361

APPLICANT

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FILING DATE

March 14, 2001

GROUP

1627

LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

AK	Hu et al., "Membrane Permeability Parameters for Some Amino Acids and β -Lactam Antibiotics Application of the Boundary Layer Approach", <u>J. Theor. Biol.</u> (1988) Vol. 131, pp. 107-114
AL	Jezyk et al., "Permeability Characteristics of Various Intestinal Regions of Rabbit, Dog, and Monkey", <u>Pharmaceutical Research</u> (1992) Vol. 9, No. 12, pp. 1580-1586
AM	Kou et al., "Calculation of the Aqueous Diffusion Layer Resistance for Absorption in a Tube: Application to Intestinal Membrane Permeability Determination", <u>Pharmaceutical Research</u> (1991) Vol. 8, No. 3, pp. 298-305
AN	Kuhfeld et al., "In Vitro Measurement of Drug Transport Using a New Diffusion Chamber Compatible with Millicell Culture Supports: Performance with Caco-2 Monolayers", <u>International Journal of Pharmaceutics</u> (1996) Vol. 133, pp. 47-58
AO	LeCluyse et al., "Strategies for Restoration and Maintenance of Normal Hepatic Structure and Function in Long-Term Cultures of Rat Hepatocytes", <u>Advanced Drug Delivery Reviews</u> (1996) Vol. 22, pp. 133-186
AP	Mathias et al., "Respiratory Epithelial Cell Culture Models for Evaluation of Ion and Drug Transport", <u>Advanced Drug Delivery Reviews</u> (1996) Vol. 22, pp. 215-249
AQ	Maurel, P., "The Use of Adult Human Hepatocytes in Primary Culture and other In Vitro Systems to Investigate Drug Metabolism in Man", <u>Advanced Drug Delivery Reviews</u> (1996) Vol. 22, pp. 105-132
AR	Pidgeon et al., "IAM Chromatography: An In Vitro Screen for Predicting Drug Membrane Permeability", <u>J. Med. Chem.</u> (1995) Vol. 38, pp. 590-594
AS	Quaroni et al., "Development of Intestinal Cell Culture Models for Drug Transport and Metabolism Studies", <u>Advanced Drug Delivery Reviews</u> (1996) Vol. 22, pp 3-52
AT	Rubas et al., "Comparison of the Permeability Characteristics of a Human Colonic Epithelial (Caco-2) Cell Line to Colon of Rabbit, Monkey, and Dog Intestine and Human Drug Absorption", <u>Pharmaceutical Research</u> (1993) Vol. 10, No. 1, pp. 113-118

EXAMINER

DATE CONSIDERED

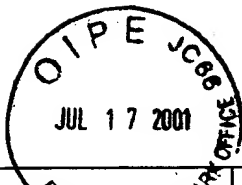
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U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

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SERIAL NO.

109904-00015

09/786,361

LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

APPLICANT

GRASS, et al.

FILING DATE

March 14, 2001

GROUP

1627

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

AU	Abstracts from <u>Pharmaceutical Research</u> (1992) Vol. 9, No. 10 - PDD 7046, Lennernas et al., "Solvent Drag and Intestinal Drug Absorption Studied by Human Intestinal Perfusion" and PDD 7048, Karlsson et al., "A New Diffusion Chamber System for the Determination of Drug Permeability Coefficients Across the Human Intestinal Epithelium that are Independent of the Unstirred Water Layer" - page S-180
AV	Abstract from <u>Pharmaceutical Research</u> (1996) Vol. 13, No. 9 - PDD 7039, McCarthy et al., "Automated Permeability Analysis of Mixtures Across Caco-2 Cell Monolayers" - page S-242
AW	Abstract from " <u>Pharmaceutical Research</u> (1996) Vol. 11, No. 10 - APQ 1113, Kuhfeld et al., "An Automated In Vitro Permeability Screen Using Robotics", page S-39
AX	Abstract from <u>Pharmaceutical Research</u> (1995) Vol. 12, No. 9 - BIOTEC 2064, Augustijns et al., "Permeability Screen for Synthetic Peptide Combinatorial Libraries Using Caco-2 Cell Monolayers and LC/MS/MS", page S-94
AY	Aarons et al., "Computer-assisted Learning Lessons in Drug Disposition and Pharmacokinetics", <u>Journal of Pharmacological Methods</u> (1988) Vol. 20, pp. 109-123
AZ	Allen, G., "MODFIT: A Pharmacokinetics Computer Program", <u>Biopharmaceutics & Drug Disposition</u> (1990) Vol. 11, pp. 477-498
BA	Amidon et al., "Model-Independent Prediction Methods in Pharmacokinetics: Theoretical Considerations", <u>Mathematical Biosciences</u> (1975) Vol. 25, pp. 259-272
BB	Amidon et al., "A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of In Vivo Drug Product Dissolution and In Vivo Bioavailability", <u>Pharmaceutical Research</u> (1995) Vol. 12, No. 3, pp. 413-420
BC	Barbalas et al., "Quantitative Selected Ion Monitoring Processing System: Software and Hardware for the Automated Collection and Analysis of Selected Ion Monitoring Data Acquired for Use in Pharmacokinetic Studies", <u>Journal of Pharmaceutical Sciences</u> (1988) Vol. 77, No. 8, pp. 679-687
BD	Barvais et al., "The Pharmacokinetics of Intravenous Anesthetic Drugs Given by Infusion: SPINA* - a Software Program", <u>European Journal of Anesthesiology</u> (1989) Vol. 6, pp. 435-447

EXAMINER

DATE CONSIDERED

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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Sheet 4 of 16

FORM PTO-1449

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

ATTORNEY DOCKET NO.

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109904-00015

09/786,361

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(Use several sheets if necessary)

APPLICANT

GRASS, et al.

FILING DATE

March 14, 2001

GROUP

1627

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

BE	Beckett et al., "A Model for Steroid Transport Across Biological Membranes", <u>J. Pharm. Pharmac.</u> (1975) Vol. 27, pp. 226-234
BF	Berger et al., "Combining Statistical, Rule-Based, and Physiologic Model-Based Methods to Assist in the Management of Diabetes Mellitus", <u>Computers and Biomedical Research</u> (1990) Vol. 23, pp. 346-357
BG	Blakey et al., "Quantitative Structure-Pharmacokinetics Relationships: I. Development of a Whole-Body Physiologically Based Model to Characterize Changes in Pharmacokinetics Across a Homologous Series of Barbiturates in the Rat", <u>Journal of Pharmacokinetics and Biopharmaceutics</u> , (1997) Vol. 25, No. 3, pp. 277-312
BH	Bois et al., "Bioequivalence: Performance of Several Measures of Extent of Absorption", <u>Pharmaceutical Research</u> (1994) Vol. 11, No. 5, pp. 715-722
BI	Bradshaw, J., "Prediction of Metabolism, Degradation and Toxicity of Xenobiotics", <u>Pesticide Sci.</u> (1992) Vol. 34, No. 2, page 185
BJ	Campbell, D.B., "Extrapolation from Animals to Man: The Integration of Pharmacokinetics and Pharmacodynamics" in <u>Cellular and Molecular Mechanisms of Drugs of Abuse</u> (1996) Edited by S. F. Ali and Y. Takahashi, pp. 116-135
BK	Cardot et al., "PKC, A New Pharmacokinetic Software Using SAS", <u>European Journal of Pharmaceutics and Biopharmaceutics</u> (1997) Vol. 43, pp. 197-199
BL	Chan et al., "Physiochemical and Drug-delivery Considerations for Oral Drug Bioavailability", <u>DDT</u> (1996) Vol. 1, No. 11, pp. 461-473
BM	Chiou, W.L., "Determination of Drug Permeability in a Flat or Distended Stirred Intestine", <u>International Journal of Clinical Pharmacology and Therapeutics</u> (1994) Vol. 32, No. 9, pp. 474-482
BN	Combrink et al., "A Comparison of the Standard Approach and the NONMEM Approach in the Estimation of Bioavailability in Man", <u>J. Pharm Pharmacol.</u> (1997) Vol. 49, pp. 731-733

EXAMINER

DATE CONSIDERED

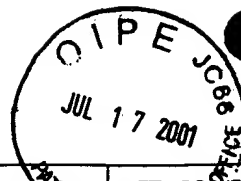
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Sheet 5 of 16



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09/786.361

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(Use several sheets if necessary)

APPLICANT

GRASS, et al.

FILING DATE

March 14, 2001

GROUP

1627

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

BO	Conolly et al., "Biologically Based Pharmacodynamic Models: Tools for Toxicological Research and Risk Assessment", <u>Ann. Rev. Pharmacol. Toxicol.</u> (1991) Vol. 31, pp. 503-523
BP	Dijkstra et al., "Simulation of Nutrient Digestion, Absorption and Outflow in the Rumen: Model Description", <u>American Institute of Nutrition</u> (1992) pp. 2239-2256
BQ	Dong, M.H., "Microcomputer Programs for Physiologically-based Pharmacokinetic (PB-PK) Modeling", <u>Computer Methods and Programs in Biomedicine</u> (1994) Vol. 45, pp. 213-221
BR	Firmer et al., "Simulation of Gastrointestinal Drug Absorption I. Longitudinal Transport in the Small Intestine", <u>International Journal of Pharmaceutics</u> (1988) Vol. 48, pp. 231-246
BS	Franck et al., "KINI: A One Compartment Intravenous Pharmacokinetic Analysis Program", <u>Computer Methods and Programs in Biomedicine</u> (1994) Vol. 42, pp. 157-165
BT	Gex-Fabry et al., "Considerations on Data Analysis Using Computer Methods and Currently Available Software for Personal Computers" in <u>Handbook on Experimental Pharmacology</u> (1994) Vol. 110, pp. 507-527 (Chapter 13)
BU	Grass et al., "A Model to Predict Aqueous Humor and Plasma Pharmacokinetics of Ocularly Applied Drugs", <u>Investigative Ophthalmology & Visual Science</u> (1993) Vol. 34, No. 7, pp. 2251-2259
BV	Grass et al., "Evaluation of the Performance of Controlled Release Dosage Forms of Ticlopidine Using In Vitro Intestinal Permeability and Computer Simulations", <u>Journal of Drug Targeting</u> (1994) Vol. 2, pp. 23-33
BW	Grass, G.M., "Simulation Models to Predict Oral Drug Absorption from In Vitro Data", <u>Advanced Drug Delivery Reviews</u> (1997) Vol. 23, pp. 199-219
BX	Gomeni et al., "IGPHARM: Interactive Graphic Package for Pharmacokinetic Analysis", <u>Computers and Biomedical Research</u> (1978) Vol. 11, pp. 345-361

EXAMINER

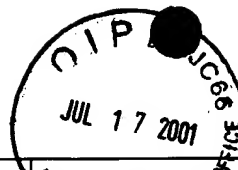
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Sheet 6 of 16



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APPLICANT

GRASS, et al.

FILING DATE

March 14, 2001

GROUP

1627

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

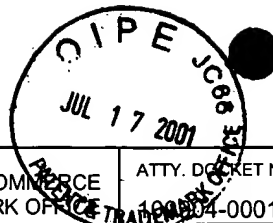
BY	Gomeni, R., "Pharm-an Interactive Graphic Program for Individual and Population Pharmacokinetic Parameter Estimation", <u>Comput. Bio. Med.</u> (1994) Vol. 14, No. 1, pp 25-34
BZ	Hampton et al., "Comparison of MS-DOS and Macintosh Pharmacokinetic Analysis Programs Using a Two-Compartment, Two-Infusion Dosing Scheme", <u>Clinical Pharmacy</u> (1991) Vol. 10, pp. 206-209
CA	Hayashi et al., "Pharmacokinetic Analysis of Cimetidine Plasma Concentration Data in Dogs Using a Two Phase Absorption Model", <u>Pharmaceutical Research</u> (1994) Vol. 11, No. 10, page S-420
CB	Hoang, K.T., "Physiologically Based Pharmacokinetic Models: Mathematical Fundamentals and Simulation Implementations", <u>Toxicology Letters</u> (1995) Vol. 79, pp. 99-106
CC	Idkaidek et al., "Determination of the Population Pharmacokinetic Parameters of Sustained-Release and Enteric-Coated Oral Formulations, and the Suppository Formulation of Diclofenac Sodium by Simultaneous Data Fitting Using NONMEM", <u>Biopharmaceutics & Drug Disposition</u> (1998) Vol. 19, pp. 169-174
CD	Jelliffe, R.W., "The USC*PACK PC Programs for Population Pharmacokinetic Modeling, Modeling of Large Kinetic/Dynamic Systems, and Adaptive Control of Drug Dosage Regimens" <u>Symposium on Computer Applications in Medical Care: A Conference of the American Medical Informatics Association</u> (1991) pp. 922-923
CE	Kalmaz, E.E., "Computer Modeling and Parameter Estimation for Pharmacokinetics and Toxicity Studies", <u>Journal of American College of Toxicology</u> (1996) Vol. 5, No. 6, page 607
CF	Keller et al., "Standardized Structure and Modular Design of a Pharmacokinetic Database", <u>Computer Methods and Programs in Biomedicine</u> (1988) Vol. 55, pp. 107-115
CG	Kirkup et al., "A Demonstration of Pharmacokinetics and Physiological Modelling Using a Microcomputer for Data Capture and Analysis", <u>Computer Applications in the Biosciences</u> (1986) Vol. 2, No. 4, pp. 277-282
CH	Kwon et al., "Theoretical Considerations on Two Equations for Estimating the Extent of Absorption After Oral Administration of Drugs", <u>Pharmaceutical Research</u> (1986) Vol. 13, No. 4, pp. 566-569

EXAMINER

DATE CONSIDERED

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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Sheet 7 of 16

FORM PTO-1449

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(Use several sheets if necessary)

APPLICANT

GRASS, et al.

FILING DATE

March 14, 2001

GROUP

1627

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

CI	Langguth et al., "Variable Gastric Emptying and Discontinuities in Drug Absorption Profiles: Dependence of Rates and Extent of Cimetidine Absorption on Motility Phase and PH", <u>Biopharmaceutics & Drug Disposition</u> (1994) Vol. 15, pp. 719-746
CJ	Leader et al., "Integrating Pharmacokinetics into Point-of-Care Information Systems", <u>Clinical Pharmacokinetics</u> (1996) Vol. 31, No. 3, pp. 165-173
CK	Leahy et al., "Physiologic Based Pharmacokinetic Modelling and QSAR", <u>Bioactive Compound Design: Possibilities for Industrial Use</u> , pp. 147-151
CL	Lincoln et al., "Pharmacokinetic Simulation: A Future Means for Better Control of Cancer Chemotherapy", <u>Recent Results in Cancer Research</u> , pp. 103-107
CM	Lu et al., "An Interactive Program for Pharmacokinetic Modeling", <u>Journal of Pharmaceutical Sciences</u> (1993) Vol. 82, No. 5, pp. 537-542
CN	Luner et al., "Description and Simulation of a Multiple Mixing Tank Model to Predict the Effect of Bile Sequestrants on Bile Salt Excretion", <u>Journal of Pharmaceutical Sciences</u> (1993) Vol. 82, No. 3, pp. 311-318
CO	Mazumdar et al., "A Mathematical Study of Simple Exponential Modelling in Biochemical Processes", <u>Australasian Physical & Engineering Sciences in Medicine</u> (1991) Vol. 14, No. 4, pp. 226-233
CP	Metzler et al., "Package of Computer Programs for Pharmacokinetic Modeling", <u>Biometrics, Journal of the Biometric Society</u> (1974) Vol. 30, No. 3, pp. 562-563
CQ	Metzler, C.M. "Commentary to 'Linear and Nonlinear System Approaches in Pharmacokinetics. How Much Do They Have To Offer? II. The Response Mapping Operator (RMO) Approach", <u>J. Pharmacokin, Biopharm.</u> (1988) Vol. 16, pp. 543-571
CR	Murata et al., "Pharmacokinetic Analysis of Single or Multiple-Dose Plasma Drug Concentration Data with a Microcomputer Using Multi-Fraction Absorption Models", <u>Journal of Pharmaceutical Sciences</u> (1989) Vol. 78, No. 2, pp. 154-159

EXAMINER

DATE CONSIDERED

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Sheet 8 of 16

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APPLICANT

GRASS, et al.

FILING DATE

March 14, 2001

GROUP

1627

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

CS	Nakai et al., "Evaluation of the Efficiency of Targeting of Antitumor Drugs: Simulation Analysis Based on Pharmacokinetic/Pharmacodynamic Considerations", <u>J. Drug Targeting</u> (1996) Vol. 8, pp. 448-453
CT	Nikiforidis et al., "Individualization of Theophylline Infusion Rate on the Basis of a Nonlinear Compartmental Pharmacokinetic Model", <u>European Journal of Drug Metabolism and Pharmacokinetics</u> (1997) Vol. 22, No. 3, pp. 265-276
CU	Nogami et al., "Pharmacokinetic Analysis on the Disappearance of Ethoxybenzamide from Plasma. Statistical Treatment of Data of Two Compartmental Model by a Digital Computer", <u>Chem. Pharm. Bull.</u> (1969) Vol. 17, No. 10, pp. 2097-2104
CV	Oh et al., "Estimating the Fraction Dose Absorbed from Suspensions of Poorly Soluble Compounds in Humans: A Mathematical Model", <u>Pharmaceutical Research</u> (1993) Vol. 10, No. 2, pp. 264-270
CW	Pearce et al., "A Hybrid Computer System for Pharmacokinetic Modeling I. Software Considerations", <u>Proceedings of the 1981 Summer Computer Simulation Conference</u> (1981) pp. 117-121
CX	Pearce et al., "PKDEMO - A Pharmacokinetic Demonstration Simulation Program", <u>Simulation</u> (1991) Vol. 56, No. 1, pp. 27-30
CY	Powers et al., "Automated Processing of Data from Pharmacokinetic Investigations", <u>Computers and Biomedical Research</u> (1976) Vol. 9, pp. 543-548
CZ	Primožic, S., "Pharmacokinetic Modeling and Simulation", <u>Acta Pharm. Jugosl.</u> (1990) Vol. 40, page 209
DA	Ramsay et al., "Pharmacokinetic Simulations Using STELLA: Prediction of In Vivo Performance of Oral Dosage Forms", <u>Eur. J. Pharm. Biopharm.</u> (1991) Vol. 37, No. 3, pp. 192-197
DB	Scaf, A.H.J., "Pharmacokinetic Analysis with Rugfit: An Interactive Pharmacokinetic Computer Program", <u>Biographamaceutics & Drug Disposition</u> (1988) (1988) Vol. 9, pp. 415-446

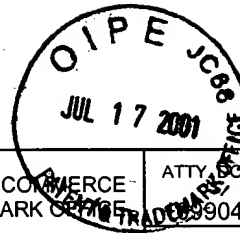
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09/04-00015

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LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

APPLICANT

GRASS, et al.

FILING DATE

March 14, 2001

GROUP

1627

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

DC	Seydel et al., "Drug-Membrane Interaction and Accumulation, Conformation Efficacy and Resistance", <u>Bioactive Compound Design: Possibilities for Industrial Use</u> pp. 137-146
DD	Staats et al., "Gastrointestinal Absorption of Xenobiotics in Physiologically Based Pharmacokinetic Models", <u>Drug Metabolism and Disposition</u> (1991) Vol. 19, No. 1, pp 144-148
DE	Stigsby et al., "A Computer Model Simulating the Intestinal Absorption of Bile Acids", <u>Gastroenterology</u> (1983) pp. 802-807
DF	Tanswell et al., "TopFit: A PC-Based Pharmacokinetic/Pharmacodynamic Data Analysis Program", <u>International Journal of Clinical Pharmacology: Therapy and Toxicology</u> (1993) Vol. 31, No. 10, pp. 514-520
DG	Taylor et al., "The Development of a Nonequilibrium Model for Computer Simulation of Multicomponent Distillation and Absorption Operations", <u>Distillation and Absorption</u> (1987) pp. B321-334
DH	Thomaseth, K., "PANSYM: A Symbolic Equation Generator for Mathematical Modelling, Analysis and control of Metabolic and Pharmacokinetic Systems", <u>Computer Methods and Programs in Biomedicine</u> (1994) Vol. 42, No. 2, pp. 73-146
DI	Timcenko et al., "Estimation of Pharmacokinetic Model Parameters", <u>JAMA Proceedings</u> (1995) pp. 47-51
DJ	Veng Pedersen, P., "Curve Fitting and Modeling in Pharmacokinetics and Some Practical Experiences with NONLIN and a New Program FUNFIT", <u>Journal of Pharmacokinetics and Biopharmaceutics</u> (1977) Vol. 5, NO. 5, pp. 513-531
DK	Veng Pedersen et al., "Perspectives in Pharmacokinetics: Linear and Nonlinear System Approaches in Pharmacokinetics: How Much Do They Have to Offer? II. The Response Mapping Operator (RMO) Approach", <u>Journal of Pharmacokinetics and Biopharmaceutics</u> (1988) Vol. 16, No. 5, pp. 543-571
DL	Veng Pedersen, P., "Mathematical and Computational Tools of Linear and Non-linear System Analysis in Pharmacokinetics", <u>Acta Pharm. J Yugosl.</u> (1990) Vol. 40, pp. 211-224

EXAMINER

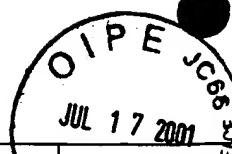
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Sheet 10 of 16



FORM PTO-1449

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499904-00015

09/786.361

APPLICANT

GRASS, et al.

FILING DATE

March 14, 2001

GROUP

1627

LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

DM	Verotta et al., "Simultaneous Modeling of Pharmacokinetics and Pharmacodynamics: An Improved Algorithm", <u>Computer Applications in the Biosciences</u> , (1987) Vol. 3, No. 4, pp. 345-349
DN	Waters et al., "Use of Computerized Data Listings and Activity Profiles of Genetic and Related Effects in the Review of 195 Compounds", <u>Mutation Research</u> (1988) Vol. 205 pp. 295-312
DO	Yang et al., "Pharmacokinetics", <u>Introduction to Biochemical Toxicology</u> , Edited by E. Hodgson and P.E. Levi, Appleton & Lange, Norwalk, CT, pp. 49-73
DP	Yu et al., "DeMons - A New Deconvolution Method for Estimating Drug Absorbed at Different Time Intervals and/or Drug Disposition Model Parameters Using a Monotonic Cubic Spline", <u>Biopharmaceutics & Drug Disposition</u> (1997) Vol. 18, NO. 6, pp. 475-487
DQ	Zhang et al., "A Computer Model for Oral Transmucosal (OT) Bioavailability Prediction", <u>Pharmaceutical Research</u> (1997) Vol. 14, No. 10, page SA-662
DR	Zhou et al., "Methodology for Using Oral Dose Pharmacokinetic Data to Select Drugs for Prolonged Release Formulations and Validation of the Method Using Simulated Data", <u>Biopharmaceutics & Drug Disposition</u> (1995) Vol. 16, pp. 319-331
DS	Abstracts from <u>Pharmaceutical Research</u> (1995) Vol. 12, No. 9, page S-367 -- PPDM 8162, Yu et al., "Saturable Small Intestinal Drug Absorption in Humans: Modeling and Interpretation of Cefatrizine Data" and PPDM 8164, Heatherington et al., "A Pharmacokinetic-Pharmacodynamic Model to Predict Effect of Formulation of Lomustine on Medullat Blastoma Cells in the CSFC:A SAAM II Simulation"
DT	Abstracts from <u>Pharmaceutical Research</u> (1992) Vol. 9, No. 10, page S-170 - PDD 7005, Crison et al., "The Effect of Particle Size Distribution on Drug Dissolution: A Mathematical Model for Predicting Dissolution and Absorption of Suspensions in the Small Intestine" and PDD 7006, Kurihara-Bergstrom et al., "Transdermal Delivery of Buprenorphine in Man"
DU	Carell et al., Abstract of "WO 95/19359," 20 Jul 1995, Derwent Database
DV	Gex-Farby et al., "Considerations on Data Analysis Using Computer Methods and Currently Available Software for Personal Computers," <u>Pharmacokinetics of Drugs</u> , Edited by Welling et al., Berlin: Springer-Verlag, pp. 507-527, 1994

EXAMINER

DATE CONSIDERED

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

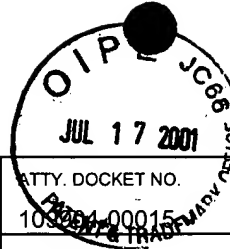
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Sheet 11 of 16



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GRASS, et al.

FILING DATE

March 14, 2001

GROUP

1627

LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	DW	Rossum et al., "Pharmacokinetics: A Dynamic Systems Approach," <u>Drug Metabolism and Distribution</u> , Edited by Lambie, Amsterdam: Elsvier Press, pp. 159-167, 1983
	DX	Harvey, "Drug Absorption, Action and Disposition," Remington's Pharmaceutical Sciences, Easton Pennsylvania: Mack Publishing Co., Chap. 35 pp. 697-724, 1990
	DY	Harvey et al., "Basic Pharmacokinetics," Remington's Pharmaceutical Sciences, Easton Pennsylvania: Mack Publishing Co., Chap. 36, pp. 725-745, 1990
	DZ	Rollins, "Clinical Pharmacokinetics," Remington's Pharmaceutical Sciences, Easton Pennsylvania: Mack Publishing Co., Chap. 37, pp. 746-756, 1990
	EA	West Database Search Report for U.S. Patent No. 5,770,384 (Androphy et al.)
	EB	West Database Search Report for U.S. Patent No. 5,789,160 (Eaton et al.)
	EC	Seydel, J.K. et al., "Quantitative Structure-Pharmacokinetic Relationships and Drug Design", <u>Pharma. Ther.</u> (1982), Vol. 15, pp. 131-181.
	ED	Enstein, Kurt, "The Future of Toxicity Prediction with QSAR", <u>In Vitro Toxicology A Journal of Molecular and Cellular Toxicology</u> , (1993) Vol. 6, No. 3 pp. 162-169
	EE	Abstract from <u>Pharmaceutical Research</u> (1994) Vol. 11, No. 10 - APQ 1113, Kuhfeld et al., "An Automated In Vitro Permeability Screen Using Robotics", page S-39

EXAMINER

DATE CONSIDERED

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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Sheet 12 of 16

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09/786.36

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APPLICANT

GRASS, et al.

FILING DATE

March 14, 2001

GROUP

1627

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NO.	DATE	NAME	CLASS	SUB- CLASS	FILING DATE
	FA	5,770,384	06/23/98	Androphy et al.			
	FB	5,789,160	08/04/98	Eaton et al.			
	FC	4,411,989	10/25/83	Grow	435	20	08/13/81
	FD	4,775,794	10/04/88	Behmann	250	373	11/02/87
	FE	4,952,061	08/28/90	Edgar	356	407	06/27/88
	FF	4,975,581	12/04/90	Robinson et al.	250	339	06/21/89
	FG	5,387,421	02/07/95	Amidon et al.	424	472	05/31/94
	FH	5,569,452	10/29/96	Amidon et al.	424	78.1	05/30/95

FOREIGN PATENT DOCUMENTS

		DOCUMENT NO.	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION YES NO PART.		
	FI	WO 94/23705	10/27/94	PCT	A61K	9/48			
	FJ	WO 96/13721	05/09/96	PCT	G01N	33/487			
	FK	WO 97/16717	05/09/97	PCT	G01N	13/00			
	FL	WO 97/20952	06/12/97	PCT	C12Q	1/68			
	FM	WO 97/22000	06/19/97	PCT	G01N	33/50			
	FN	WO 97/29091	08/14/97	PCT	C07D	223/12			
	FO	WO 97/49987	12/31/97	PCT	G01N	27/02			
	FP	WO 98/00231	01/08/98	PCT	B01J	19/00			

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

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March 14, 2001

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1627

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NO.	DATE	NAME	CLASS	SUB- CLASS	FILING DATE
	GA	6,150,416	11/21/00	KICK, et al.	514	616	
	GB	5,989,918	11/23/99	DIETZ et al.	436	63	
	GC	5,956,501	09/21/99	BROWN	395	500.32	
	GD	5,914,891	06/22/99	MCADAMS, et al.	364	578	
	GE	5,880,972	03/09/99	HORLBECK	364	496	
	GF	5,854,992	12/29/98	SHAKHNOVICH et al.	702	27	
	GG	5,808,918	09/15/98	FINK, et al.	364	578	
	GH	5,807,879	09/15/98	ROSENBROUGH	514	387	

FOREIGN PATENT DOCUMENTS

		DOCUMENT NO.	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION YES NO PART.		
	GI	EP 0 818 744 A2	01/14/98	EUROPE	A61K	9/48			
	GJ	EP 0 918 296 A1	05/26/99	EUROPE	G01N	33/487			

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

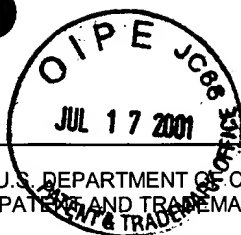
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09/786.361

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APPLICANT

GRASS, et al.

FILING DATE

March 14, 2001

GROUP

1627

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NO.	DATE	NAME	CLASS	SUB- CLASS	FILING DATE
	HA	5,705,335	01/06/98	HENDRY	435	6	
	HB	5,703,792	12/30/97	CHAPMAN	364	496	
	HC	5,699,268	12/16/97	SCHMIDT	364	496	
	HD	5,657,255	08/12/97	FINK, et al.	364	578	
	HE	5,625,579	04/29/97	HINSBERG, III et al.	364	578	
	HF	5,579,250	11/26/96	BALAJI, et al.	364	496	
	HG	5,331,573	07/19/94	BALAJI et al.	364	500	
	HH	4,335,438	06/15/82	SMOLEN	364	497	

FOREIGN PATENT DOCUMENTS

		DOCUMENT NO.	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION YES NO PART.		

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

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108904-00015

09/786.361

LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

APPLICANT

GRASS, et al.

FILING DATE

March 14, 2001

GROUP

1627

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

EF	Notification of Transmittal of the International Search Report or the Declaration, November 1, 2000, International Application No. PCT/US99/21001
EG	Written Opinion, February 26, 2001, PCT/US99/21001
EH	Notification of Transmittal of International Preliminary Examination Report, December 14, 2000, International Application No. PCT/US99/21151
EI	Written Opinion, July 7, 2000, International Application No. PCT/US99/21151
EJ	Notification of Transmittal of the International Search Report or the Declaration, February 4, 2000, International Application No. PCT/US99/21151
EK	Abstract: Holford, N.H.G. "Drugmodel", 1981
EL	Abstract: Agrafiotis D. K.; Myslik J. C.; Salemme F. R., "Advances in diversity profiling and combinational series design", Accession Number 1999254287, 1999
EM	Abstract: Ajay; Bemis, Guy W.; Murcko, Mark A., "Designing Libraries with CNS Activity", 1999
EN	Abstract: Cho S J; Zheng W; Tropsha A, "Focus-2D: a new approach to the design of targeted combinatorial chemical libraries", 1998, Accession Number 1998362517
EO	Abstract: Hopfinger A. J.; Duca J.S., "Extraction of pharmacophore information from high-throughput screens"

EXAMINER

DATE CONSIDERED

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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